Medical Progress

Chronic Urticaria

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Urticaria affects 15% to 20% of the population once or more during a lifetime. Chronic urticaria is a frequent recurrent eruption over a period greater than 6 weeks; the cause remains a mystery in more than 75% of cases. Urticaria and angioedema may be produced by immunologic or nonimmunologic means. Urticarial vasculitis, contact urticaria, mastocytosis, physical urticarias, dermatographism, cholinergic urticaria, localized heat urticaria, cold urticaria, aquagenic urticaria, and vibratory angioedema all require specific evaluation and treatment. Chronic idiopathic urticaria is usually controlled by antihistamines; depending on the circadian rhythm of the eruption, sedative or nonsedative antihistamines are prescribed. Some patients will require a combination of H_1 and H_2 antagonists, or even parenteral corticosteroids.

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Patients with urticaria and angioedema are commonly seen in medical practice, and those who render care should have knowledge of the types of urticaria and angioedema and their common causes and treatments.

Approximately 15% to 20% of the population experience one or more episodes of urticaria during their lifetime. The cutaneous appearance is easy to recognize, and many patients will have made their own diagnosis before presenting for treatment. Common urticarial lesions consist of pruritic erythematous papules, plaques, or wheals that vary from about a millimeter to several centimeters or larger in size. They may show central clearing, and their form may take on unusual serpiginous shapes. The lesions may be found on any part of the body. Individual cutaneous lesions are usually transient, lasting less than four hours. If particular lesions remain longer than 12 to 24 hours, the possibility of underlying vasculitis must be considered. Lesions of angioedema differ in that they are often not pruritic and consist of deeper dermal and subcutaneous swellings that most frequently involve the lips and eyelids. Angioedema often accompanies urticaria in its various forms but may occur by itself. Serious consequences may result if the edema involves such structures as the larynx. Lesions of urticaria and angioedema may be associated with systemic symptoms from direct visceral involvement or due to the release of circulating chemical mediators. These mechanisms may lead to diverse symptoms such as hoarseness, respiratory distress, abdominal pain, nausea, vomiting, diarrhea, arthralgias, headache, and hypotension. Even neurologic symptoms, such as seizures, have been associated with angioedema.

Histologically, urticarial wheals exhibit dermal edema with a sparse dermal perivascular lymphocytic infiltrate that may contain eosinophils. The predominant lymphocytes are activated $CD4^+$ T cells expressing DR surface markers. Under the electron microscope, degranulated mast cells and eosinophils are seen. Biopsy specimens of angioedematous areas show similar findings except that the edema and infiltration extend into the subcutis. A histologic study done on 43 patients with chronic urticaria revealed that their lesional skin contained ten times the normal number of mast cells and monocytes.[1] No explanation for the accumulation of these cells was apparent, but it has long been known that the mediators of urticaria are mast cell products.

The human dermis has between 7,000 and 12,000 mast cells per cubic millimeter. On toluidine blue-stained sections, these cells are identified by the presence of metachromatic oval granules, which may measure as much as 0.5 nm. Electron microscopy of these membrane-surrounded granules reveals a crystalline structure of scrolls, lattices, and gratings.

Several substances are known to induce the release of mediators from mast cells, including immunoglobulin (Ig) E, biologically active peptides (C3a, C5a, and lysosomal granule proteins), polymers (compound 48/80, dextran), enzymes (chymotrypsin, phosphatidases), and many other miscellaneous factors, including drugs and physical stimuli (Table 1). One human mast cell has about 300,000 binding sites for IgE. Dimerization of surface IgE through antigen bridging results in mast cell activation, including membrane lipid methylation, activation of adenylate cyclase, and the uncovering of a serine esterase activity. Granule-bound chemical mediator release is dependent on cyclic adenosine monophosphate (cAMP) and calcium. Activation of cutaneous mast cells results in the release of primary mediators of inflammation (preformed, granule-associated) and the release of secondary mediators of inflammation.

Although many mediators may play a role in the production of urticaria, histamine appears to be the primary mediator involved in most cases of acute urticaria. Injection of histamine will reproduce the symptoms and signs of urticaria, and administering antihistamines will relieve them. The cutaneous response to the intradermal administration of histamine is exemplified by the triple response of Lewis. Initially vasodilation begins in the area of injection, followed

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ABBREVIATIONS USED IN TEXT
cAMP = cyclic adenosine monophosphate
Ig = immunoglobulin

by a surrounding flare due to axon reflex. The transudation of fluid from the vessel to the extravascular compartment results in tissue edema, appreciated clinically as urticaria or angioedema. This histamine-mediated effect is attributed to the widening of the space between endothelial cells, allowing the passage of material from the intravascular to the extravascular compartments. Both eosinophils and polymorphonuclear leukocytes have positive chemokinetic movement in response to H_1 and H_2 agonists, but H_2-receptor effects appear to be inhibitory and H_1 stimulatory when assessing directed migration of each cell type to a preferred chemotactic factor.

The biologic effects of histamine follow its interaction with two specific classes of receptors on target cells, the so-called H_1 and H_2 receptors. A production of leaky venules attributed to a partial disconnection of endothelial cells is due to both H_1- and H_2-receptor effects.

Various leukocytes, including eosinophils and lymphocytes, have histamine receptors. Histamine through H_1 receptors appears to increase the expression of receptors for the C3b component of complement on human eosinophils. Suppressor T lymphocytes have H_2 receptors, and histamine appears to inhibit the development of a cytotoxic response.

Eosinophilic chemotactic factors of anaphylaxis consist of two closely related tetrapeptides that, when released by mast cells, result in the attraction of eosinophils and an increase in C3b receptors on eosinophil cell membranes. These factors are both chemotactic for eosinophils and deactivating for these cells once they have been attracted. Although these factors may have some chemoattractant effect on other granulocytes, these effects seem to be preferential for eosinophils. Eosinophilic chemotactic factors of anaphylaxis probably act by attracting eosinophils to a site, holding them there by deactivation, and then facilitating immune adherence and phagocytic functions.

Heparin is another granule-associated factor released by mast cells. The local effects of this substance include the stimulation of endothelial cell chemotaxis and proliferation, the augmentation of histaminase activity, and an inhibition of several steps of complement activation.

There are several chemical mediators released by the mast cell that do not exist preformed, as do the granule-associated factors, but are produced in response to mast cell stimulation. Platelet-activating factor(s) is produced in response to a stimulation of mast cells and results in the aggregation and release of serotonin from platelets. Several lipid factors are also produced by stimulated mast cells, including leukotrienes, which are more potent vasoactive substances than histamine.

Many other mediators—including kinins and kallikrein, acetylcholine, fibrinogens, and prostaglandins—may possibly cause or contribute to wheal formation in various situations. Intermediate-molecular-weight eosinophil chemotactic factors, which are released in a linear fashion with histamine, have been found. High-molecular-weight neutrophil chemotactic factor has been identified in the venous effluent of patients with cold urticaria. This substance deactivated neutrophils in a time- and dose-dependent manner.

Common Urticaria

For the purposes of this discussion, we will review the types of urticaria that are more commonly seen.

Urticaria is conveniently divided into acute and chronic types. Chronic urticaria refers to a frequently recurring urticaria over a period of greater than six weeks. Whereas the cause for acute urticaria is commonly ascertained, the inciting agent remains a mystery in more than 75% of cases of chronic urticaria (Table 2). Unlike chronic urticaria, acute urticaria is more likely to be mediated through an IgE mechanism. Furthermore, acute urticaria is usually found in young patients, as opposed to the chronic form that has been reported most frequently in middle-aged women.

Urticaria and angioedema may be produced by immunologic or nonimmunologic means. Immunologic mechanisms involve either type I (IgE-mediated, immediate hypersensitivity), type II (cytotoxic antibody-mediated), or type III (immune complex-mediated) reactions. Type II and type III events may lead to complement activation and the release of the anaphylatoxins, C3a and C5a, which provoke mast cell degranulation. These anaphylatoxins may also be more directly produced by the action of bacterial lipopolysaccharide on the alternative complement pathway. In addition, inflam-

TABLE 1.—*Nonimmunologic Histamine Releasers*

Polymers	Chemicals or Drugs
Dextran	Aspirin
Compound 48/80	Alcohol
Calcium ionophore A23187	Opiates
Bacterial toxins	Polymyxin B sulfate
Snake venoms	Colistin sulfate
Biologic polypeptides	Thiamine hydrochloride
Ascaris species	Tyramine
Jellyfish	Tubocurarine chloride
Portuguese man-of-war	Quinine sulfate
Spines and hairs of caterpillars	Radiographic dyes
Nettles	Scopolamine hydrochloride
Moths	Gallamine triethiodide
Foods	Dexamethonium
Shellfish	Stilbamidine isethionate
Strawberries	Chlortetracycline bisulfate
Egg white	Amphetamines
	Hydralazine hydrochloride
	Tolazoline hydrochloride
	Cinnamaldehyde
	Cinnamic acid
	Benzoic acid
	Sodium benzoate

TABLE 2.—*Causes of Urticaria*

Drugs	Physical agents
Foods	Dermatographia
Inhalants	Pressure
Infections	Cold
Insect bites	Cholinergic agents
Internal diseases	Solar light waves
Vasculitis	Heat
Mastocytosis	Water
Contactants	Vibration

matory responses to immune complexes may eventuate in the elaboration of other chemical mediators that promote vasodilation and plasma exudation, such as the kinins, prostaglandins, and leukotrienes, and contribute to the production of edematous wheal-like lesions.

Nonimmunologic mechanisms usually involve substances that directly incite the release of histamine and other mediators from mast cells. A list of such agents is given in Table 1. In addition, aspirin, which does not release histamine directly, has been shown to aggravate the eruptions in 20% to 40% of patients with chronic urticaria. Though aspirin may cause urticaria, its main effect is enhancement, an effect that may last as long as three weeks after ingestion. This mechanism is not well understood, but it is postulated that the action may be due to the ability of aspirin and other nonsteroidal anti-inflammatory drugs to inhibit prostaglandin synthesis.

Prostaglandins of the E series interact with mast cells to elicit increases in cAMP levels, which decreases mediator release. A decrease in prostaglandin E production may enhance release and may also cause more arachidonic acid to be metabolized through the lipoxygenase pathway, which is unaffected by aspirin. This second pathway leads to leukotriene compounds with potent vasodilatory, exudative, and bronchospastic effects of their own. In addition, salicylates have been shown to inhibit a step in one pathway of histamine catabolism. Aspirin-sensitive patients have an increased incidence of urticarial reactions to azo dyes and benzoic acid, which are frequent food additives, and to nonsteroidal anti-inflammatory drugs.

Drugs taken parenterally or orally are among the most common causes of urticaria. Also, urticarial reactions make up a substantial percentage (23%) of all cutaneous drug reactions. Nearly any drug may be an inciting agent, and immunologic (types I and III) or nonimmunologic mechanisms may be responsible. Common offenders include penicillin, cephalosporins, aminoglycosides, sulfonamides, serum, dextran, polypeptide hormones, barbiturates, hydralazine, phenylbutazone, tranquilizers, hydantoins, quinine, and mercurial diuretics.

Most drugs and simple chemicals are of low molecular weight and are unable to stimulate the immune system unless they react irreversibly with proteins to form multivalent drug-protein complexes. Drugs such as penicillin that are easily able to react with proteins are immunogenic.

Penicillin is the most common urticaria-producing drug on an allergic basis. The average incidence of IgE-mediated penicillin allergy is about 2%, and life-threatening complications occur in 2% to 13% of these. Reactions may be divided by the time of onset after administration into immediate (15 to 20 minutes), accelerated (30 minutes to 48 hours), and delayed (after 2 days). Extremely small amounts of the drug may elicit hypersensitivity phenomena in sensitive persons. Coleman and Swineford reported the case of a patient in whom an intradermal injection of only 5 μU precipitated a systemic reaction.[2] There is also a report of a case of urticarial eruption in a woman who presumably absorbed penicillin through her vaginal mucosa from the semen of her sexual partner who was taking penicillin. It is particularly important to remember that traces of penicillin are frequently found in milk and other dairy products.

In patients with a history of "penicillin reaction," previous skin testing may effectively screen for IgE-mediated sensitivity. Skin testing is carried out using the major determinant, which represents 95% of metabolized penicillin (penicilloyl-polylysine [Pre-Pen]) and the minor determinant mix (not generally available) or a dilute solution of penicillin G (10,000 U per ml). The minor determinants are more frequently associated with anaphylaxis than the major determinants, so it is important to use either the minor determinant mix or dilute penicillin G in addition to penicilloyl-polylysine. Scratch tests should be applied before intradermal testing to avoid serious reactions. Test sites are examined for wheals after 15 to 20 minutes; if positive, the use of β-lactam antibiotics should be avoided (penicillin, semisynthetic penicillins, and cephalosporins). In certain life-threatening infections, however, these antibiotics are required. Sullivan and associates detailed a successful oral desensitization regimen used for patients with endocarditis, *Pseudomonas* species sepsis or pneumonia, or staphylococcal infections that required the use of penicillin or semisynthetic penicillins.[3] Parenteral desensitization techniques have also been used, but Sullivan and colleagues point out that some cases of anaphylaxis and more cases of urticaria have resulted from parenteral desensitization.

Food and food additives are probably too frequently implicated in urticaria. Common urticariogenic foods include shellfish, fish, eggs, nuts, chocolate, berries, tomatoes, cheese, and milk. In a recent study only 1.9% of the reactions had a food-linked origin.[4] Frequent food additives or contaminants include azo dyes, benzoic acid, penicillin, yeasts, citric acid, and salicylates. Some of these act nonimmunologically and some act through IgE hypersensitivity. Tyramine, a phenolic amine, is found in foods such as lobster and scallops and in foods changed by bacteria, molds, or yeasts. It induces histamine release nonimmunologically and is also catabolized by one of the enzymes that catabolizes histamine and may compete with histamine for degradation. This substance may be responsible for the urticariogenic effect of these foods, bacteria, and fungi.

Inhalant allergens, including pollens, spores, animal danders, and dust inhalants, have been rarely reported to produce urticaria. This route of exposure may be a significant problem, however, as evidenced by Tannenbaum's patient in whom, following exposure to a wide variety of substances, severe angioedema developed, making it impossible for her to leave her house.[5]

Infections of many diverse types have been associated with urticaria. Some commonly associated viral infections include hepatitis B (often with preicteric symptoms of serum sickness) and mononucleosis. Immune complex mechanisms have been shown to be important in these diseases. Dermatophyte and candidal infections can also be urticariogenic. Some dermatophyte antigens may cross-react with airborne molds (*Alternaria* and *Cladosporium*), and, therefore, skin tests for immediate reaction to *Trichophyton* species may be positive in persons allergic to molds. Parasitic infections are frequently searched for but rarely found in patients with recurrent urticaria. There have been reports of urticarial eruptions with giardiasis, amebiasis, trichomoniasis, malaria, and scabies. Localized bacterial infections, such as sinusitis, dental apical infections, and gastrointestinal tract infections, may, on occasion, elicit urticarial eruptions.

Insect-bite hypersensitivity, particularly hymenoptera

sensitivity, can be an important allergic cause of urticaria, angioedema, and anaphylaxis. The hymenoptera are divided into two families, the Apidae (honeybees and bumblebees) and the Vespidae. The Vespidae are further divided into the genera *Polistes* (wasps) and *Vespula* (hornets and yellow jackets). Many patients are sensitive to the venom of insects from both families, as diagnosed by skin tests.

Many varieties of internal diseases are associated with urticaria. Hormonal disturbances have occasionally been implicated, particularly thyroid autoimmunity.[6] A few cases of progesterone hypersensitivity have also been reported. In these cases, exacerbations occurred monthly, seven to nine days before the menses, the times of peak progesterone levels. Urticaria and angioedema have also been reported in rheumatic fever, rheumatoid arthritis, lymphoreticular malignancy, and carcinoma. Of the collagen vascular diseases, systemic lupus erythematosus is most commonly associated with urticaria, as it is found in 6.9% to 13% of cases.[7,8] In lupus, the wheals are often produced by type III immune complex mechanisms, and eruptions often occur concurrently with fever, decreased complement levels, increased erythrocyte sedimentation rate, and increased disease activity. A lesional biopsy usually reveals vasculitis.

Immunofluorescence studies have shown deposition of the major basic protein of eosinophils in lesions from patients with chronic idiopathic urticaria, episodic angioedema, and facial edema. Major basic protein causes a release of histamine from human basophils and induces wheal-and-flare reactions on intradermal injection.[9] Neutrophilic urticaria is characterized by a neutrophilic venulitis without fibrinoid necrosis, hemorrhage, or leukocytoclasia. Results of laboratory studies are normal. Patients respond to antihistaminic agents. The histologic features and the therapeutic course of these patients are compatible with a phase or type of chronic urticaria.[10]

Urticarial Vasculitis

Urticarial vasculitis is an interesting disorder first brought to light by McDuffie and co-workers, who reported on four patients with urticarial-appearing eruptions that showed necrotizing vasculitis on biopsy.[11] The authors attributed the findings to an immune complex syndrome.

Clinically the lesions appear similar to common urticarial wheals, except that the individual lesions remain for longer than 24 to 72 hours. They may show petechiae or purpura, particularly as they resolve. Residual pigmentary changes and scaling may be noted. The lesions may be pruritic or painful, and patients may have angioedema.

Associated symptoms are most often rheumatologic—arthralgias and arthritis—in cases reported, but a wide spectrum of disease severity has been noted from mere cutaneous eruptions to severe systemic involvement. A substantial percentage of patients have shown hypocomplementemia, and there is evidence for activation of both the classical and alternative complement pathways. The erythrocyte sedimentation rate is the laboratory test most frequently giving abnormal results, and it is elevated in most patients. This test may be the most useful screening device for vasculitis in urticaria.

Histologically, vasculitis shows endothelial swelling with fibrin deposition. Vessels may be occluded. The cellular infiltrate usually shows a predominance of polymorphonuclear leukocytes with nuclear fragmentation (leukocytoclasia). Immunoglobulin and complement deposits are found in early lesions. In view of the many mediators of inflammation that produce vasodilation and exudation and the anaphylatoxin effects of complement components C5a and C3a, it is not surprising that this type of lesion could exhibit urticarial features clinically.

The possibility of underlying vasculitis should be considered in patients with chronic urticaria. Some researchers have estimated the percentage of underlying vasculitic causes to be at 20%, but others found vasculitis in biopsy specimens of only 1 of 43 patients with chronic urticaria.[1,12] Corticosteroids, salicylates, and immunosuppressive agents in various combinations have been used to treat urticarial vasculitis. Indomethacin has been used successfully. Nevertheless, some authors think that no treatment has been particularly effective. Besides this group of patients with urticarial vasculitis of unknown cause, patients can be seen, as previously mentioned, with vasculitis in urticarial lesions associated with preicteric hepatitis B, serum sickness, collagen vascular diseases, mononucleosis, and in selective C1q deficiency. Hepatitis B is an important consideration if a patient presents acutely with serum sickness-like symptoms of urticaria, arthralgias, proteinuria, hematuria, and, sometimes, angioedema.

Contact Urticaria

Contact urticaria consists of a wheal-and-flare response to substances applied to intact skin. The reaction usually occurs within 20 to 30 minutes. Once again, the mechanism may be immunologic, nonimmunologic, or unclassifiable, but allergic types generally involve a type I mechanism. Both types are best diagnosed by open patch tests observed for 30 minutes for allergic and for 45 minutes for nonallergic urticarial reactions. Table 3 lists implicated allergic contact urticariogens. Maibach and Johnson divided allergic contact urticaria into four stages[13]: stage 1 shows local urticaria; stage 2 is when there is urticaria plus angioedema; stage 3 involves urticaria plus asthma, rhinoconjunctivitis, and gastrointestinal or orolaryngeal dysfunction, which has rarely been pro-

TABLE 3.—*Causes of Allergic Contact Urticaria*

Acrylic monomer	Hair sprays
Aminothiazole	Horse serum
Ammonia	Lindane
Animal dander	Monoamylamine
Arthropods	Nail polish
Benzophenone	Penicillin
Benzoyl peroxide	Perfumes
Carrots	Phenylmercuric propionate
Castor beans	Platinum salts
Cat saliva	Potatoes
Cephalosporins	Silk
Cetyl alcohol	Sodium sulfide
Chlorpromazine	Spices
Cobalt chloride	Stearyl alcohol
Cod liver oil	Streptomycin
Diethyltoluamide	Sulfur dioxide
Dog saliva	Taliphatic polyamide
Estrogenic creams	Tetanus antitoxin
Exotic woods	Wheat
Flour	Wool
Formaldehyde	

duced by patch testing; and stage 4 refers to urticaria plus anaphylaxis. These reactions have reportedly been caused by substances such as penicillin, mechlorethamine, epoxy resin, neomycin, chloramphenicol, amino phenazone, bacitracin, and the ubiquitous balsam of Peru (found in cosmetics, soaps, deodorants, and perfumes). The mechanism (or mechanisms) by which balsam of Peru causes contact urticaria is controversial. As opposed to the allergic and unspecified types, nonimmunologic contact vasoactive mediator release is rarely a serious problem but may be more common. Offenders include benzoic acid, dimethyl sulfoxide, cinnamaldehyde, balsam of Peru, benzocaine, sorbic acid, ethyl alcohol, butyric acid, sodium benzoate, and acetic acid. Keeping cinnamaldehyde in mind is useful because many mouthwashes and toothpastes contain this compound; it may, therefore, be a cause of lip and oral mucosal swelling. Ammonium persulfate is an urticariogen that acts by an unknown mechanism. Though urticaria from contacts is uncommon, the possibility should be borne in mind when a patient presents acutely without any internally administered identifiable cause.

Mastocytosis

Mastocytosis denotes the presence of increased numbers of mast cells in a variety of organs. Skin involvement alone is most frequent and often is asymptomatic. The other organs that can be involved include bone, gastrointestinal tract, liver, lymph nodes, and spleen. There is no sex predominance, and heredity does not appear to be a factor. Mastocytosis usually presents in infants and small children, most showing signs by age 2. It occurs less commonly in adults, although they are more likely to have systemic involvement. Symptoms are produced by degranulation of the overabundant mast cells leading to local or systemic symptoms due to circulating mast cell mediators, particularly histamine.

Cutaneous mastocytosis is referred to also as urticaria pigmentosa. The most common appearance is of red-brown macules and papules over the trunk and extremities. A peculiar adult form, telangiectasia macularis eruptiva perstans, shows diffuse pigmented, telangiectatic macules. A rare erythrodermic form also has been noted. Solitary mastocytomas occur at birth or in early infancy. Stroking lesions of urticaria pigmentosa will produce whealing (Darier's sign), and patients may have a considerable problem with dermatographism. Flushing or pruritus may be triggered by temperature changes, exercise, hot baths, stress, stroking, or drugs (particularly nonimmunologic histamine releasers). Histologically, all types show mast cells infiltrating the upper third of the dermis or scattered in tumorlike dense aggregates.

Systemic mastocytosis is seen in approximately 10% of all patients with mastocytosis, and there is occasionally an absence of skin lesions. The skeletal system and the gastrointestinal tract are the most common sites. Symptoms of attacks include intense pruritus, headache, diarrhea, bronchospasm, rhinorrhea, flushing, hypotension, nausea, vomiting, tachycardia, dyspnea, and syncope, and the condition may sometimes resemble the carcinoid syndrome. Rarely, hemorrhagic episodes may be associated with mast cell heparin release. Elevations of urinary histamine, its metabolite, 1-methyl-4-imidazoleacetic acid, or serum histamine may aid in the diagnosis. Abnormalities of these values may be found in either cutaneous or systemic disease, although urinary histamine cannot always be relied on to relate to disease activity.

Treatment in mild cases requires only H_1-blocking antihistamines. The addition of the H_2 blocker, cimetidine, has given some patients increased relief from cutaneous and gastrointestinal symptoms and appears to be preferable to using either alone.

Cromolyn sodium has proved to be an effective treatment for systemic mastocytosis in a double-blind study and for cutaneous mastocytosis in a single-blind trial.[14,15] Its mechanism of action is unknown, but an inhibition of mast cell degranulation has been postulated.

Another therapeutic modality involves an inhibition of prostaglandin biosynthesis. Mast cells release a quantity of prostaglandin D_2. Roberts and associates correlated elevated urinary levels of a prostaglandin D_2 metabolite with flushing, hypotension, and tachycardia in two patients.[16] In one patient with uncontrolled life-threatening attacks, the addition of aspirin to his antihistamine regimen alleviated his symptoms almost entirely. There is danger, however, in the use of aspirin or other nonsteroidal anti-inflammatory agents, as idiosyncratic exacerbations have occurred. Theoretically, blocking the biochemical pathway leading to the prostaglandins may divert more arachidonic acid into the formation of leukotrienes, which are potent vasodilatory and bronchospastic agents.

A final treatment modality in cutaneous disease that combines photosensitizers (psoralens) with long-wave ultraviolet light has been beneficial to some. Granerus and colleagues correlated decreased symptoms with a decrease in the major urinary metabolite of histamine after using this therapy.[17]

Physical Urticarias

Urticaria and angioedema may be induced by physical agents, such as stroking, pressure, cold, light, heat, water, and vibration. Some of these stimulants act through IgE-mediated mechanisms, as shown by the Prausnitz-Küstner (passive transfer) reaction. Physically provoked reactions may be responsible for 7% to 17% of cases of chronic urticaria.[18] Though they are not usually the cause of significant morbidity or mortality, they occasionally can be, and health care providers should be aware of their existence.

Dermatographism

It is important to recognize dermatographism, a common form of urticaria, because it may be mistaken for common urticaria. Although some degree of reaction to stroking the skin is found in about half the population, the rapid appearance of a wheal at the site of firmly stroked skin is found in 1.5% to 4.24% of normal persons.[19] The wheal usually fades within 30 minutes. This immediate response can be IgE-mediated, with demonstrably positive passive transfer tests. Occasionally the response is frequent and severe enough to be symptomatic. Dermatographism is common enough to coexist with other forms of urticaria. Patients with more severe forms of the disorder, who have exquisite sensitivity to pressure on the skin, may present with a more typical urticarial appearance, and the clue to the contrary is the predisposition for lesions to appear where clothing rubs the skin. Patients with mastocytosis or the hypereosinophilic syndrome are predisposed to dermatographism. They usu-

ally have a notable decrease in symptoms with the use of antihistamines, such as hydroxyzine hydrochloride, cyproheptadine hydrochloride, or diphenhydramine hydrochloride. Giving aspirin, indomethacin, or cimetidine has not been beneficial.

A much less common type of dermatographism has a delayed onset, occurring 1 to 8 hours after the stimulus, and is often a tender, deeper swelling that lasts 24 to 48 hours. The mechanism is unknown, and passive transfer has not been accomplished. This disorder may occasionally be difficult to distinguish from delayed pressure urticaria.

Pressure Urticaria or Angioedema

Pressure urticaria or angioedema may occur immediately, or a delayed type may occur four to six hours after pressure is applied. The lesions may last as long as 48 hours, and they have a refractory period of 24 to 48 hours. The deep swellings are often tender and may be associated with malaise and a viral-like syndrome of aches. Frequent sites are under straps, belts, or on the palms and soles.

The common activities that induce delayed pressure urticaria are standing, working, or sitting on a hard surface, using a screwdriver or hammer, hand clapping, carrying a handbag, wearing tight-fitting clothing, dental work, kissing, sexual intercourse, and tampon usage. Delayed pressure urticaria is slightly more common in men. Antithyroid microsomal antibodies are found in 30% of patients. The lesions are morphologically similar to classic late-phase cutaneous reaction. In patients who had skin tests positive to food allergens, none lost their delayed pressure reactivity while on a diet omitting the food allergens to which they gave positive reactions. This disease cannot be cured by eliminating the "offending agents" from the diet. The diagnosis of delayed pressure urticaria can be easily made by dermographometric testing. Delayed dermatographism may be the same disorder as delayed pressure urticaria induced by a different method of pressure application. Parenteral corticosteroid therapy remains the only known effective treatment for disabling delayed pressure urticaria, knowing that too often the high doses required will induce unacceptable side effects.[20-22]

Cold Urticaria

Cold urticaria has the potential of being a life-threatening disease, making it important to recognize. In this usually acquired type of urticaria, patients with exposure to a decrease in ambient temperature will have hives develop at the time of cooling or on rewarming. Extreme and even fatal reactions have occurred when affected persons emerge from swimming in cold water.

Acquired cold urticaria is the most common form seen. This disease results in whealing of the skin after exposure to cold contact or cold immersion. This usually occurs minutes after rewarming, and the wheals last from one to two hours. In some persons, the mucous membranes are affected, and cold stimulation can result in a swollen tongue.

A few patients with cold urticaria have associated cryoproteins, such as cryoglobulins, cryofibrinogens, cold hemolysins, and possibly cold agglutinins. These are factors that should be sought in the workup of a new patient with cold urticaria. They are thought to induce urticaria by inducing the complement factors C3a and C5a. Some patients with acquired cold urticaria do not have a cryoprotein but do have an associated circulating immune globulin. Passive transfer has been shown for some subjects. The serum factor most often appears to be IgE, although IgM and IgG have also been implicated.

The usual test for cold urticaria is a three- to five-minute application of an ice cube to forearm skin. During the rewarming phase, a wheal occurs that conforms to the area cooled.

Leukotriene E_4 and histamine levels, when measured in the blood draining the site of a cold challenge in patients with clinical histories of cold urticaria, were increased after a typical clinical response to the challenge. No increase in leukotriene E_4 or histamine levels was observed following a cold challenge in nonresponding persons.[23]

Cyproheptadine hydrochloride is the standard antihistamine used for symptomatic relief. Acquired cold urticaria lasts months to years, and patients must be cautious about cold exposure.

Familial cold urticaria is a rare, usually autosomal dominant condition that is associated with burning wheals appearing 30 minutes to 3 hours after exposure to a cold wind. The urticaria usually lasts for 48 hours. It is characteristically accompanied by fever and leukocytosis and sometimes arthralgias and headache. The mechanism of this disease is unknown.

Cholinergic Urticaria

Cholinergic urticaria is the second most common after dermatographism. The pruritic lesions are distinctive, consisting of tiny 2- to 3-mm wheals with surrounding flares. These wheals develop in response to exercise or warm temperatures, which, in some cases, may be associated with angioedema, bronchospasm, and anaphylaxis. Symptoms indicative of cholinergic stimulation may also occur. Elevated plasma histamine levels, which peaked at 20 to 25 minutes, have been found in some patients. Soter and co-workers found an increased release of histamine, as well as chemotactic factors for eosinophils and neutrophils.[24] The cutaneous response may be mediated by cholinergic sympathetic nerve fibers and may indirectly lead to mast cell degranulation. Confirmatory intradermal skin testing may be attempted using acetyl-β-methylcholine or nicotinic acid tartrate, but these tests are positive in only about a third of the patients with the disease, and the results are not always reproducible. Commens and associates emphasized that provocation by exercise or a hot bath is much more effective than skin tests.[25] It is notable, however, that Sheffer and colleagues have possibly distinguished a new syndrome of exercise-induced anaphylaxis that occurs with angioedema and urticaria and in which there are sizable increases in serum histamine levels.[26] Others have shown similar cases that occurred only in a strict time relation to meals.

Antihistamines, particularly hydroxyzine hydrochloride, are relied on for the treatment of cholinergic urticaria; however, because refractory periods of as long as 24 hours can sometimes be induced by a reaction to a hot bath or exercise, daily exercise has been used as a method of preventing attacks.

Solar Urticaria

Solar urticaria occurs within minutes after exposure to light of various wave lengths and fades 15 minutes to 3 hours after it begins. This abnormal response to light has occasionally been seen in cases of systemic lupus erythematosus,

porphyria cutanea tarda, erythropoietic protoporphyria, and polymorphous light eruption. Monochromatic phototesting, including the use of a new instrument called a "spectrodermograph," has allowed classification of this disease by eliciting the wave length. Most commonly, patients react to wave lengths in the sunburn range—290 to 320 nm. Positive passive transfer has been found in this group and in those who react in the range of 400 to 500 nm. Some have postulated that antibody may react with a photoproduct, leading to mast cell degranulation. Because Soter and co-workers found increased histamine and chemotactic factors for neutrophils and eosinophils in venous blood after light challenge,[24] it is not surprising that a few patients may experience wheezing, dizziness, and headache after lengthy exposures.

Treatment should involve avoiding the harmful light wave lengths. Antihistamines may be useful; β-carotene is useful in some patients but does not protect against long wave or visible light. The development of tolerance to light may occur with repeated exposures. Psoralens plus ultraviolet light (PUVA) therapy has been found useful by some. Ravits and colleagues recommend the use of combinations of induced pigmentation, oral β-carotene, and antihistamines.[27]

Localized Heat Urticaria

In localized heat urticaria, a rare form of physical urticaria, localized, pruritic wheals occur within minutes of heat contact and may last as long as an hour. Provocative testing is done with a metal tube filled with hot water. Passive transfer attempts have been unsuccessful. Histamine and other mast cell mediators may be involved in the response, but the mechanism remains unknown. Studies by Tóth-Kása and associates suggest that chemosensitive nerve endings may be needed to allow the response.[28] Some authors have reported finding complement abnormalities in one patient that were indicative of alternative pathway activation.[29] Treatment with antihistamines has been helpful to some patients but not to others.

Aquagenic Urticaria

Patients with aquagenic urticaria, an uncommon type, experience the formation of pruritic wheals that are often follicular in skin areas that have come in contact with water. Clinically, the morphology may be difficult to distinguish from that of cholinergic urticaria. The length of contact needed to produce lesions has varied from minutes to half an hour. Other solvents, such as ethanol or acetone, do not induce aquagenic urticaria. The mechanism may involve acetylcholine, as topical scopolamine abolished the wheal production.[30] In addition, histamine levels were increased in venous drainage from the stimulation site.

Antihistamine treatment may give partial control, but the benefit has been inconsistent; cyproheptadine and promethazine hydrochloride were more efficacious than chlorpheniramine maleate and hydroxyzine hydrochloride.

Vibratory Angioedema

Vibratory angioedema was first described by Patterson and co-workers in a family in whose members localized swelling developed after five minutes of contact with a vibratory stimulus.[31] The swellings lasted hours to days and were sometimes associated with headache. The inheritance pattern suggested autosomal dominant transmission. Sporadic

TABLE 4.—*Commonly Used Antihistamines (H_1 Blockers)*

'Classical' Antihistamines	*'New Generation' Antihistamines*
Alkylamines	
Chlorpheniramine maleate*	Acrivastine†‡
Dexchlorpheniramine maleate (Polaramine)	
Brompheniramine maleate (Dimetane)	
Tripolidine hydrochloride (Actidil)	
Ethanolamines	
Diphenhydramine hydrochloride*	Ketotifen fumarate (Zaditen)‡
Dimenhydrinate*	Oxatomide (Tinset)‡
Clemastine fumarate*	
Cinarrizine (Midronal)‡	
Ethylenediamines	
Tripellenamine (Pyribenzamine) citrate, hydrochloride	
Piperazines	
Hydroxyzine hydrochloride,* pamoate*	Cetirizine hydrochloride (Zyrtec)†‡§
Meclizine hydrochloride*	
Phenothiazines	
Promethazine hydrochloride*	Mequitazine (Primalan)†‡§
Piperidines	
Cyproheptadine hydrochloride (Periactin)	Loratadine (Claritin)†§
Azatadine maleate (Optimine)	Astemizole (Hismanal)†§
	Terfenadine (Seldane)†
	Azelastine hydrochloride‡
Tricyclics	
Doxepin hydrochloride*	
Amitriptyline hydrochloride*	
Imipramine hydrochloride*	
Desipramine hydrochloride*	

*Several manufacturers produce this drug.
†Nonsedative.
‡Not available in the United States (April 1989).
§Once-a-day dosage.

cases have also been reported. Using a laboratory vortex as a method of stimulation, Kaplan and Beaven demonstrated elevated venous histamine levels from the area, stimulated within a minute of the application of vibration.[32] Complement levels in these patients are normal, and passive transfer has not been accomplished. No therapy other than the avoidance of vibration has been useful.

Treatment

In all cases of urticaria, a search for the inciting agent must be made, but as mentioned above, in patients with chronic urticaria, this is frequently fruitless. Elimination and readdition diets may be helpful. Patients found to be sensitive to salicylates, tartrazine, or benzoates should attempt to eliminate these items. This may be difficult or impossible, however, as these are not only additives but occur naturally as well. In 1981 a review listed drugs that contain tartrazine.[33]

Nonphysical urticarias may also be aggravated by external vasodilatory influences, such as heat, exercise, sunburn, vasodilating drugs, fever, stress, and alcohol. If possible, these should be avoided.

In general, H_1-blocking antihistamines are the mainstay of therapy for acute and chronic urticaria. Their antagonism of histamine is competitive and reversible. These compounds are readily absorbed in the gastrointestinal tract.

The antihistamines are categorized by chemical type, though the basic substituted ethylamine structure, present also in histamine, is common to most (Table 4).

Two broad groups of antihistamines can be used to treat chronic urticaria: "classical," sedative ones, often available over-the-counter, and new, nonsedative, available by prescription only, and expensive. Most classical antihistamines act rapidly, will control cholinergic urticaria owing to their anticholinergic and antiserotonin activities but can be responsible for long-lasting somnolence, and their use is incompatible with everyday activities. Most nonsedative antihistamines, such as terfenadine, astemizole, loratadine, and cetirizine hydrochloride, are slower acting than classical or traditional antihistamines, but some, such as astemizole, can protect a patient for a number of days, thereby reducing the total cost of the treatment.[34-37]

Some patients respond to the use of classical antihistamines with central nervous system stimulation at conventional doses and complain of restlessness and insomnia; this is mostly the case at both ends of the lifespan—that is, infants and toddlers, and elderly patients. Rarely, small doses may evoke epileptic seizures in patients with focal central nervous system lesions. Antihistamines themselves rarely evoke systemic allergic reactions. It is important to remember that ethylenediamine and diphenhydramine are potent contact sensitizers (delayed type IV hypersensitivity). If a patient is sensitized to one of these, ingestion could lead to widespread drug eruption or cause a previously quiescent dermatitis to flare. The ethylenediamine antihistamines, as well as hydroxyzine, can cross-react with ethylenediamine. Aminophylline preparations also contain this compound. If a patient does not respond to the use of one antihistamine, it is best to choose another that is in a different chemical category. Increasing the dose will only produce side effects. Combining two antihistamines is not recommended.

Among the most potent, and probably the most useful, antihistamines for treating chronic urticaria are the tricyclic antidepressants, doxepin hydrochloride, amitriptyline hydrochloride, and imipramine hydrochloride.[38,39] Their side effects, however, should be seriously considered: anticholinergic effects with blurred vision, urine retention, dryness of the mouth, and the like. Any underlying psychiatric disease warrants the opinion of a specialist. Shertzer and Lookingbill recommended using hypnosis and relaxation therapy in patients with chronic urticaria[40]; compared with baseline and control session values, a hypnosis session provided relief of pruritus, but there was no change in the number of hives. At a follow-up examination of 15 patients a year after the completion of experimental sessions, 6 were free of hives and another 7 reported improvement.[40]

Because human skin blood vessels contain H_2 as well as H_1 receptors and an H_2 agonist can lead to wheal formation, there is a good rationale for using the H_2 blocker, cimetidine, as an adjunct in treating chronic urticaria. Combination therapy using both H_1 and H_2 blocking agents has met with varying success.[41] Cimetidine should not be used alone, however, and H_2 blockade may negate the feedback inhibition of histamine itself on mast cell degranulation, which is mediated through the H_2 receptor.

Ortolani and associates showed some benefit during challenge tests of cromolyn sodium in patients with chronic urticaria who were sensitive to aspirin and tartrazine.[42] Inhibitors of mast cell degranulation (terbutaline sulfate, ketotifen fumarate), used in conjunction, led to improvement in ten patients with chronic urticaria. Epinephrine is transiently helpful, especially in patients with severe bouts of acute urticaria. Not only does this drug help to decrease cutaneous vasodilation, but it also inhibits mast cell degranulation by raising cAMP levels.

Topical corticosteroids are not efficacious in urticaria, but parenteral corticosteroids have been used. The rationale for their use is not clear in histamine-mediated urticaria, but when other mediators are implicated, their use may be plausible. Corticosteroids do inhibit the release of arachidonic acid from cellular phospholipids, thus inhibiting the conversion of arachidonic acid into both prostaglandins and leukotrienes. Furthermore, in types of urticaria mediated by type III immune complex reactions or other mechanisms involving complement activation, parenteral steroids may be useful. Stanozolol appears to act synergistically with glucocorticosteroids, and used together they may be capable of inducing remission in some patients, requiring the use of parenteral steroids to control angioedema.[43]

In summary, urticaria and angioedema are cutaneous and subcutaneous reaction patterns that may be precipitated by a host of mechanisms. In addition, lesions that may be identical in clinical appearance to the types described above may be seen in patients with other diseases as varied as bullous pemphigoid, erythema multiforme, rashes of pregnancy—prurigo gestationis of Besnier, pruritic urticarial papules, and plaques of pregnancy—and the gyrate erythemas. A multitude of chemical mediators, many probably yet undiscovered, may be important factors in evoking cutaneous responses such as these.

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